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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/468,610	06/06/95	BURTON	S 010055-134

18M2/0819
GENENCOR INTERNATIONAL INC.
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WEBER EXAMINER	
ART UNIT	PAPER NUMBER
1808	

DATE MAILED:

08/19/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.
08/468,610

Applicant(s)
Burton et al.

Examiner
Jon P. Weber

Group Art Unit
1808



☒ Responsive to communication(s) filed on 8 Apr 1996

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-5 and 7-23 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-5 and 7-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Art Unit 1808

Claims 1-5 and 7-23 have now been presented for examination.

The response with amendments filed 08 April 1996 has been received and entered. Claim 6 has been canceled by the amendment.

5 The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10 The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

15 The proposed amendment would limit the claimed invention to binding proteins to the matrix at a pH value of the medium of "5 or more". Support for this amendment is allegedly at page 29, lines 24-28 and in Example X(a) (binding at pH 9.1). While a pH of 9.1 is certainly above 5, there is no clear support for the specific limitation of "5 or more". At page 29, the disclosure states that the groups begin to titrate and become charged between a pH value of 5 and 9. Hence, at just above pH value of 5 it is expected that the resin is charged and the claimed process is inoperative. The only purpose of the limitation is to
20 circumvent the specific disclosure of Sasaki et al. (1979) and (1981) which discloses binding proteins at a pH value of 4.5 to Amberlite CG-50.

Art Unit 1808

Claims 1-5 and 7-23 are rejected under 35 U.S.C. § 112,
first paragraph, for the reasons set forth in the objection to
the specification. This is a new matter rejection. The new matter
must be deleted or the response prove that the amendment is not
5 new matter.

Claims 1-5 and 7-23 stand rejected under 35 U.S.C. § 103 as
being unpatentable over Sasaki et al. (1979) or Sasaki et al.
1981) in view of Kasche et al. (1990), Teichberg (1990) and Jost
10 et al. (1974).

It is argued that Sasaki et al. is in error in asserting
that the resin is not charged when the protein binds to it. It is
argued that the Declaration of Becker demonstrates that the resin
is charged when the protein is bound. Hence, it is urged that
15 Sasaki et al. do not disclose the claimed process. Further it is
urged that Sasaki et al. operate at a pH of 4.5 for protein
binding which is lower than the newly added limitation of binding
at a pH of 5 or more.

It is argued that each of Kasche et al. (1990), Teichberg
20 (1990) and Jost et al. (1974) bind protein under conditions where
the resin is charged as opposed to the claimed process.

At the interview of 01 February 1996, newly assigned
examiner did not have sufficient time to carefully consider the
Declaration or the relied upon references which had been lost

Art Unit 1808

from the parent case, 08/268,178. The allegations set forth in the response were taken at face value, and the interview summary should be considered in this light. The references and Declaration have now been carefully considered.

5 Each of the references is alleged to be defective because the binding of protein occurs at a pH where the resin is charged as opposed to using only hydrophobic properties. The Declaration of Becker is the sole evidence provided against Sasaki et al.

10 The titration in Sasaki et al. (1979) of Amberlite CG-50 is provided in Figure 1, and described also at page 1539, column 1. The resin is washed thoroughly with 2 N HCl then 2 N NaOH and water (to obtain the Na⁺ form), suspended in water or 0.5 M NaCl that has been boiled to remove dissolved carbon dioxide, and the pH adjusted to 11 with carbonate free 50% NaOH prior to titration
15 with standardized 0.2 N HCl.

20 The titration of Becker is set forth in the appendix to the Declaration in USSN 08/268,178. The resin is suspended with 1 M NaOH until the pH was stable and 1 M HCl until the pH was stable then washed with water and dried. The resin was then suspended in 0.010 M or 0.5 M NaCl and titrated with 0.1 M standardized NaOH. The pH was allowed to equilibrate between additions of base.

 The Declaration of Becker is not a true side by side comparison with Sasaki et al.; the titrations run in opposite directions. Sasaki et al. use acid to titrate the conjugate base

Art Unit 1808

form of the resin, while Becker et al. use base to titrate the acid form of the resin. Sasaki et al. was careful to assure that the starting pH was a certain value and removed dissolved carbon dioxide from the titrant so that it would not compromise the titration. Becker does not attempt to remove carbon dioxide from the titrant and does not start the titration at a certain pH. It is not clear that the pH of the solution has any clear meaning at the beginning of the titration of Becker.

The only reason Becker gives for asserting that his titration is superior to Sasaki et al. is that Sasaki et al. do not calculate the empirical charge data from the titration curve as Becker allegedly does. The conversion of the titration data in Appendix II into the numbers in Appendix I are not disclosed. Hence, it is not clear how to evaluate the calculation. It is important to note that mere equivalents of base added to the resin is not the same thing as the charge on the resin. The partial charge on the resin at any pH within the "buffer region" (± 1 pH unit from the pKa) can be readily calculated from the pKa and the Henderson-Hasselbach equation. Outside the "buffer" region the charge can be calculated by more rigorous methods. Hence, if the determination of the pKa of 6.1 of Sasaki et al. is correct, then asserting negligible charge of the resin at pH 4.5 is valid.

Art Unit 1808

As a consequence, the assertion of Becker that Sasaki et al. is incorrect does not appear to be well founded. Further, the opinion of Becker et al. is given little weight in view of what appears to be superior analytical methodology of Sasaki et al. and the lack of evidence to support the opinion.

Absent the Declaration of Becker, the assertion that Sasaki et al. (1979) did not bind the protein to the resin under conditions where the resin is uncharged cannot be affirmed. Further evidence that the resin in Sasaki et al. (1979) is not relying upon charge for protein binding is set forth at page 1540 second full paragraph, "the absorptions of pancreas enzymes on Amberlite CG-50 were hardly affected by ionic strength". Sasaki et al. (1979) go on to say that by pH 5.5 about 30% of the carboxyl groups are charged and the enzymes were hardly absorbed.

While it is true that in the disclosures of Kasche et al. (1990), Teichberg (1990) and Jost et al. (1974), proteins are bound to the resin while partial charges were still present, these references still embody the basic concept of the claimed invention. Hydrophobic binding, albeit slightly abetted by ionic binding, of proteins to the matrix is followed by elution under conditions where the matrix is clearly charged (Kasche et al., 1979, page 150, first paragraph). The additional references expand the pH regime and resin functional groups that can be used in the hydrophobic-ionic chromatography technique of Sasaki et

Art Unit 1808

al. (1979). In Teichberg (1990) the hydrophobic interaction is with the affinity ligand, whereas in Jost et al. the hydrophobic interaction is with the spacer arm. As a consequence, these references can be seen to expand the resins and groups that can be considered for hydrophobic-ionic chromatography.

In Sasaki et al. (1982) the discussion and Figure 5 clearly set out the general mechanism of hydrophobic-ionic chromatography. It is clear that Sasaki et al. contemplate generalizing the technique beyond the specific example of Amberlite CG-50. It is suggested that if the matrix absorbent carried alkaline groups, then the chromatography would have an opposite pH relationship.

The arguments filed 08 April 1996 have been fully considered but they are not deemed to be persuasive. The rejection under 35 U.S.C. § 103 is adhered to for the reasons of record at pages 3-4 of the Office action of 03 October 1995 and the additional reasons above.

No claims are allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

Serial Number: 08/468,610

-8-

Art Unit 1808

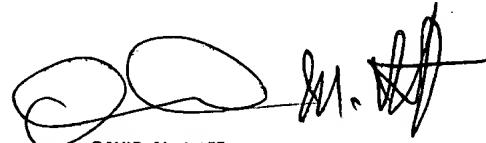
5 A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL
ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS
ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS
OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION
IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED
STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE
ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE
PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE
MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE
10 STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM
THE DATE OF THIS FINAL ACTION.

15 Any inquiry concerning this communication should be directed
to Jon P. Weber, Ph.D. at telephone number (703) 308-4015. The
examiner can normally be reached during the hours of 06:30 to
16:30 Eastern (off first Friday).

20 If attempts to reach the examiner by telephone are
unsuccessful, a message may be left on the voice mail. The fax
number for Art Unit 1808 is (703) 305-7401. Any inquiry of a
general nature or relating to the status of this application
should be directed to the Group receptionist whose telephone
number is (703) 308-0196.

Jon P. Weber, Ph.D.

J.P.W. 06 August 1996


DAVID M. HOFF
PRIMARY EXAMINER
ART UNIT 1808